III. REMARKS

Claim Status

Claims 1-16 and 21 have been cancelled. Claims 17-18 and 22-33 are active in the case. Claims claims 29 and 33 are withdrawn from consideration as being directed to a non-elected invention. Claims 17-18, 22-28, and 30-32 are currently under consideration. Claims 18, 27 and 31 have been amended.

Claim Rejections - 35 U.S.C. § 112, second paragraph

Claims 17-18, 22-28 stand 30-32 stand rejected under 35 U.S.C. 112, second paragraph, in that the preamble of claim 27 is unclear. Claim 27 is drawn to treating a mammal suffering from or is at increased risk of developing sepsis or septic shock.

It is unclear to the examiner whether the method is drawn to treating a mammal suffering from a risk of developing sepsis or septic shock, or if the method treats a mammal suffering from sepsis or septic shock. Therefore the metes and bounds of the preamble are unclear and clarification is required to overcome the rejection.

The claims in question are drawn to a method of treating a mammal suffering from a risk of developing sepsis or septic shock and to a method of treating a mammal suffering from sepsis or septic shock. It is clear that the two methods are alternative since an animal already suffering from sepsis or septic shock cannot be at risk of developing something it already has.

Further, the examiner states that the phrase "at increased risk of developing sepsis or septic shock" in claim 27 is a

relative term which renders the claim indefinite.

Applicant has deleted the word "increased" to obviate the basis for this rejection.

The method is drawn to either Claim 30 claiming the peptide comprising SEQ ID NO:2 or claim 31 claiming the peptide having the amino acid sequence of SEQ ID NO:2. It is unclear to the examiner what the difference between the claims are since both claims recite "open" language.

Claim 30 is intended to encompass peptide which are, in whole or in part, the SEQ ID NO:2. Claim 31 is intended to encompass only those compositions where the peptide portion is identical to SEQ ID NO:2.

Claim 31 has been amended to clarify its meaning.

Claim Rejections - 35 USC § 102

Claims 18, 22, 23, 25, 27-31 stand rejected under 35 U.S.C. 102(b) as being anticipated by Quarfordt et al., J. of Biological Chem. 1982. Vol. 257(24): 14642-14647.

Quarfordt et al. is cited as teaching purifying human apolipoproteins, including apolipoprotein CI (apoCI) where the apoCI has the sequences of applicant's claims 27-28.

Quarfordt et al. is further cited as teaching administering apoC apoproteins with pharmaceutically acceptable adjuvants by perfusion to the liver of a mammal [rats] where Table I shows the injected activity of perfused apoCI in combination with apolipoprotein E is significantly less than that of C-III-2 and somewhat better than that of C-II in lipid recovery.

Quarfordt et al. is also cited as teaching preparations of

pharmaceutical compositions comprising triglyceride emulsions having ApoCI.

Therefore the examiner concludes Quarfordt et al., teach the instant claims.

Applicant respectfully disagrees.

In summary, Quarfordt et al. discloses that the composition of apoCI is known, and that it is a member of the group of apolipoproteins comprising C-I, C-II, C-III and E.

As stated by the examiner, Quarfordt discloses the results of administering C apolipoproteins by perfusion to rat livers and demonstrates the effect on triglyceride metabolism. Quarfordt treats all the livers with each of 3 C apolipoproteins, with or without apolipoprotein E, and notes that C-III-2 had the greatest inhibitory effect.

As stated by Quarfordt et al., the presence of C apolipoproteins, particularly C-III-2, in the perfusate produced a significant increase in the total recovery of radiolabeled lipid. This disclosure clearly leads one skilled in the art to consider the C apolipoproteins as being equivalent at best or to consider C-III-2 as preferable.

This disclosure of C proteins generically and the absence of any reason to utilize apolipoprotein C-I would not lead to the present invention. Applicant has found the it is not the total level of apoC proteins that is important - it is only the amount of apoCI that is important. Applicant's figure 1 shows the relation between apoCI in blood plasma and its relation to sepsis. Most importantly, Figure 3 demonstrates that while apoCI is effective, apoCIII is hardly effective at all.

In summary, the administration of any apoC protein does not function to mitigate shock or sepsis responses in a mammal. It is only apoC1 that is effective and only if administered in a therapeutic shock or sepsis mitigating amount.

Thus, Quarfordt et al. does not suggest or disclose applicant's method of mitigating shock or sepsis responses in a mammal.

The examiner responds by citing the doctrine that a well known process of administration of a well known composition does not become patentable upon the discovery of a new property for that same composition citing *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999) and *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) for the proposition that claiming a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable.

However, a key antecedent to the application of the doctrine of inherency is that the "characteristic is a necessary feature or result of a prior-art embodiment...") Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) [emphasis supplied]

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)* (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art).

To establish inherency, the extrinsic evidence "... must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981).* [emphasis supplied]

Applying the precedents to the facts of the present case, Querfordt et al. discloses the genus of apolipoproteins of which applicant's claimed species is a member. Applicant disclosed species have a property not present in all the members of the genus and are used in a novel process where the usefullness of the claimed process depends on the provision of a therapeutically effective sepsis or shock reducing amount of the claimed species.

The determination that there is a shock reducing amount of the specifically claimed species of the known genus is not within the ability of one skilled in the art because, absent hindsight knowledge of the fact that the claimed species is effective for the claimed purpose of ameliorating sepsis or shock, the skilled practitioner would not even be led to do the experiments, however simple or complicated, to determine the parameters of the process.

Thus, applicant does not believe the examiner has demonstrated that all the elements of the claimed process were disclosed by Quarfordt et al. (*inter alia*, claimed species, shock reducing amount, injection instead of perfusion) and

respectfully requests favorable reconsideration of this ground for rejection.

Claim Rejections - 35 USC § 103

Claims 17-18 and 22-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Oosten et al., (J. of Biol. Chem. 2001. Vol. 276(23): 8820-8824) in view of Quarfordt et al., (J. of Biological Chem. 1982. Vol. 257(24): 14642-14647).

As cited by the examiner Oosten et al., teach that apoE may be used therapeutically to protect against LPS-induced endotoxemia also known as sepsis and that lipopolysaccarides (LPS) are a component of gram-negative bacteria which is the primary cause of gram-negative sepsis.

Oosten et al., teach that all lipoproteins bind endotoxins and that combining lipoproteins with LPS before administration to mammals protects against endotoxin induced death (page 8820, col.2

However Oosten et al, do not teach administering SEQ ID NO:11.

Applicant respectfully disagrees. The finding by van Oosten et al. that apoE binds to the LPS of bacteria is not basis for predicting that apoC1 would have the same effect.

Not all apolipoproteins that have an effect on the lipid uptake in the liver have an effect on LPS binding (which is only logical considering that these are two different working mechanisms). This can be illustrated by the fact that one of the

apolipoproteins, apoCIII, is able to inhibit the apoE-dependent uptake of lipid particles in the liver but has no effect at all on sepsis related phenomena.

In his Table 1, Quarfordt et al. only show that combinations of apoCl and apoE have an effect on the uptake of lipid particles by liver cells. From this alone it is not possible to draw a conclusion about the effect of the individual components.

Even assuming arguendo, that this is the case, the effects of apoCl on uptake in liver cells is not predictive of the effects of apoCl in sepsis (or rather the immune response to toxic components of bacteria).

The working mechanism of apoC1 in sepsis is not through uptake (via an LDL receptor) as is the case with lipid uptake by the liver, but through binding to the toxic LPS of bacteria and the effects of this binding on the response generated via the TOLL-like receptor that mediates the immune response to these toxic components.

Further, although both apoE and apoC1 are apolipoproteins, they differ enormously:

1] they do not show a significant homology in their amino acid sequence,

2] apoE is 5 times as big as apoC1 and

3] the domains of apoE and apoC1 that bind to the LPS are completely different.

The direct teaching of van Oosten et al. as set forth above to a person skilled in the art is that apoE is able to bind the

LPS of bacteria. But it would not be obvious to suggest that apoCl would have a similar effect.

First of all, the molecules differ too much to suggest a similar working mechanism based on structural similarities. Secondly, the publication of Quarfordt et al. would not be taken into consideration by a person of skill since the effects on liver uptake have nothing to do with the effects on sepsis. It is respectfully suggested the any suggestion of obviousness (which as demonstrated above is absent) could only be based on impermissible hindsight.

The examiner concludes that one of ordinary skill in the art would have a reasonable expectation of success by including apoCI within the composition of method of treatment because the art teaches the administration of ApoC1 and ApoE together.

Applicant respectfully points our that the administration of apoCI and apoE as taught in the art is taught for an unrelated purpose, functioning through an unrelated biological pathway and thus there would be no motivation to try one or both of the components of the combination in response to a shock or sepsis condition. And since there would be no motivation to combine and experiment there would be not experimentation to find an appropriate does since no does would have been though effective for sepsis or shock.

Favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for

any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

NORRIS McLAUGHLIN & MARCUS, P.A.

By /Serle I. Mosoff/

Serle Ian Mosoff
Attorney for Applicant(s)
Reg. No. 25,900

875 Third Avenue - 18th Floor
New York, New York 10022
Phone: (212) 808-0700
Fax: (212) 808-0844